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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,886	10/31/2003	Tetsuo Tsuji	0032-0284P	9003

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,886	TSUJI ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 07/976,457.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *31 October 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Claims 1-8 are pending and under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 31 October 2003 has been considered by the examiner. A signed copy is attached.

Biological Deposit

3. Applicants' Declaration as to the deposit of the hybridomas secreting antibodies of the invention is noted as being acknowledged in USSN 08/236,013.

Specification

4. The title of the invention is not descriptive of the invention claimed. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Immunoassay for hBNP.

Claim Objections

5. Claims 4 and 7 are objected to because of the following informalities: Claim 4 recites "the immunoassay of claim 1, herein said second antibody..." It appears that a "w" is missing from the word "wherein". The word tense for the work "produce" is should be changed to past tense. The claim should read "...wherein said first antibody is produced..." Appropriate correction is required.

Obviousness-Type Double Patenting

6. Claims 1-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 7-11 and 17-19 of U.S. Patent No. 6,677,124 (hereinafter the '124 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to an immunoassay comprising a sandwich ELISA wherein the claimed protein is human brain natriuretic protein (hBNP) and the claimed antibodies are to the C-terminal region of hBNP and N-terminal region of hBNP.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as

follows: instant claim 1 is obvious over claim 7 of the '124 patent. Instant claims 2 and 5 are obvious over claim 10 of the '124 patent. Instant claim 3 and 7 are obvious over claim 11 in the '124 patent. Instant claim 4 is obvious over claims 8 and 18 in the '124 patent. Instant claim 6 is obvious over claim 17 of the '124 patent. Instant claim 8 is obvious over claim 19 of the '124 patent. The '124 patent claims a first antibody as being produced by hybridoma BC203, FERM BP-3515 (claim 8) and the second antibody as being produced by hybridoma KY-hBNP-II, FERM BP 2863 (claim 11). The instant application claims the first antibody as being produced by hybridoma KY-hBNP-II, FERM BP-2863 (claim 3) and the second antibody as being produced by hybridoma BC203, FERM BP-3515 (claim 4). As such, the instant application merely recites the same immunoassay as the '124 patent with the same antibodies in reverse presentation, where one antibody is called the "first" antibody and the other, the "second" antibody. Both methods of sandwich immunoassay are well known and routine and provide the same results. The first antibody is immobilized in the '124 patent. In the instant claims, either the first or second antibody can be immobilized (see instant claim 1, steps (a) and (b)). Thus, claims 1-8 of the instant application read on subject matter that is not patentably distinct from the '124 patent.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a first monoclonal antibody and a second antibody that is polyclonal or monoclonal, does not reasonably provide enablement for a first antibody that is polyclonal or monoclonal and a second antibody that is monoclonal or polyclonal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1, 6, and 8 generically recite an immunoassay using two antibodies which recognize two different regions of hBNP, with one region being the C-terminal region, the last 6 amino acids of which are SEQ ID NO: 2 (KVLRRH) [amino acids 27-32 of hBNP]. The disclosure, as filed, does not support the use of the generic language in which the antibodies (either monoclonal or polyclonal) recognize two different regions of hBNP. The disclosure only supports an assay in which one monoclonal antibody recognizes the C-terminal region of hBNP, with the other antibody recognizes another portion of hBNP (i.e. the N-terminal region). The specification discloses that the immunoassay for hBNP is characterized in that hBNP is sandwiched between the monoclonal antibody A and an antibody B (which can be either

monoclonal or polyclonal) that recognizes hBNP at the site different from that recognized by said antibody A (specification p. 6, first paragraph).

The only type of sandwich immunoassay enabled by the specification is one in which one of the monoclonal antibodies is immobilized on a solid-phase, i.e. a heterogeneous assay. This permits washing of the complex, performance of the assay without prior sample cleanup and increased sensitivity. It would require an undue amount of experimentation by one skilled in the art to perform the assay without the use of a solid-phase (i.e. using two polyclonal antibodies) that would provide all of the benefits of the instant invention without guidance from the applicants.

Claims 2-5, and 7 are rejected as being dependent on claim 1.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

9. Claims 1-3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art, at the time the application was filed, that Applicants were in possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 1, 6, and 8 generically recite an immunoassay using two antibodies which recognize two different regions of hBNP, with one region being the C-terminal region, the last 6 amino acids of which are SEQ ID NO:2 (KVLRRH) [amino acids 27-32 of hBNP]. The disclosure, as filed, does not support the use of the generic language in which the antibodies recognize two different regions of hBNP. The disclosure only supports an assay in which one monoclonal antibody recognizes the C-terminal region of hBNP, with the other antibody recognizing another portion of hBNP (i.e. the N-terminal region). The specification discloses that the immunoassay for hBNP is characterized in that hBNP is sandwiched between the monoclonal antibody A and an antibody B [which can be monoclonal or polyclonal] which recognizes hBNP at the site different from that recognized by said antibody A (specification p. 6, first paragraph). Claims 2-5, and 7 are rejected as being dependent on claim 1.

The claimed subject matter must be described in the specification to ensure that applicant had in his possession, as of the filing of the application, the specific subject matter claimed. See

In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass*, 492 F.2d 1228, 181 USQ 31 (CCPA 1974).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession f the invention. The invention is, for purpose of the 'written description' requirement, whatever is now claimed." (See p. 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See *Vas-Cath,* at 1116). As discussed above, the skilled artisan cannot envision the detailed amino acid structure of the encompassed homologous polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See, *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

10. Claims 3-5 and 7 recite the limitation "said first (or second) antibody" in the claims and. There is insufficient antecedent basis for these limitations in the claims.

11. Claim 2 recites the limitation "said Fab' fragment" appears to refer to an epitope. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1,2, 6, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itoh et al., (Endocrinology, 1990 Sep;127(3):1292-1300) in view of Takeyama et al., (1990 Jul 3;130(2):217-22), Sutcliffe et al., (1983 Feb 11;219(4585):660-6), Harlow et al., (Antibodies, A Laboratory Manual. 1988. Cold Spring Harbor Laboratory. pp 578-582), Hashida et al., (Clinica Chimica Acta 1988 175:11-1), and Bulinski (Intl Rev Cytology 1986;103:281-302).

Claims 1, 6, and 8 recite an immunoassay using two antibodies which recognize two different regions of hBNP, with one region being the C-terminal region, the last 6 amino acids of which are SEQ ID NO:2 (KVLRRH) [amino acids 27-32 of hBNP]. Claim 2 recites the immunoassay of claim 1 wherein the Fab' fragment of an antibody which is reactive with the first region of hBNP recognizes the intramolecular disulfide bridged loop structure of hBNP.

Itoh et al., teach the production of monoclonal antibodies to brain natriuretic peptide (BNP) (p. 1293, column 1), their application in radioimmunoassays, and that monoclonal antibodies are useful tools for the elucidation of the physiological and pathophysiological significance as a neuropeptide and as a hormone (see abstract). Itoh et al., also disclose that polyclonal antibodies have several disadvantages, such as their limited supply and their contamination with irrelevant antibodies not directed towards BNP, and that the monoclonal antibody technique has now come into widespread use for the study of various substances

including biologically active peptides (p. 1293, column 1, first full paragraph). The monoclonal antibodies produced by the authors, KY-BNP-I and KY-BNP-II possess high affinity for BNP and are presumed to recognize the N-terminal portion of BNP, as the C-terminal fragment of BNP did not show significant cross-reactivity in either RIA (p. 1297, column 2). Itoh et al., also teach a monoclonal antibody that recognizes the intramolecular disulfide bridged loop (identified as the "ring structure of hBNP" on p. 6, first paragraph) of hBNP (see p. 1294, column 2, fourth paragraph, and Figure 1). Itoh et al., do not teach the use of antibodies to the C-terminal fragment (residues 27-32) of human BNP in sandwich assays.

Takeyama et al., teach the amino acid sequences of porcine and human BNP (p. 218, Figure 1). Takeyama et al., also teach that the amino acid sequence of BNP has a high sequence homology with atrial natriuretic peptide (ANP) (p. 218).

Sutcliffe et al., teach that peptide immunogens can be used for eliciting reagents with predetermined specificity that can be used for basic research (see abstract).

Harlow et al., teach the practice of the sandwich immunoassay. Harlow et al., teach that the sandwich technique is one of the most useful immunoassays, that they are quick, accurate, specific, and that the major advantage is that the antigen does not need to be purified prior to use (p. 579, first and second paragraphs). Harlow et al., also teach that the assay requires two antibodies that bind to non-overlapping epitopes on the antigen, such as two monoclonal antibodies that recognize discrete sites (p. 579, first paragraph).

Hashida et al., teach an enzyme immunoassay for α-human atrial natriuretic polypeptide (a 28 amino acid polypeptide). In this assay, polystyrene balls were coated with monoclonal IgG specific for the N-terminal half of the disulfide bond ring structure of α-hANP and rabbit Fab' specific for the C-terminal (17-28) of α-hANP was conjugated to horseradish peroxidase, in which the sample was first added to the immobilized antibody (p. 12, Introduction). Hashida et al., also teach that the C-terminal half of α-hANP was raised in rabbits by immunization with α-hANP (17-28)-bovine thyroglobulin conjugate (p. 13).

Bulinski teaches that methods for preparation and use of peptide antibodies are simple and well established and that the peptide used is from 6-10 residues in length, although success has been achieved with much smaller or longer peptides (p. 286).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use hBNP as taught by Takeyama et al., to produce monoclonal antibodies specific for BNP, as taught by Itoh et al., because Takeyama et al., teach that the amino acid sequence of hBNP is known, and Itoh et al., provides an expectation of success by demonstrating that BNP is

antigenic. It would have also been obvious to produce monoclonal antibodies that are reactive with the C-terminal portion of hBNP because Sutcliffe et al., teach that peptide immunogens can be used for eliciting reagents with predetermined specificity that can be used for basic research and Bulinski teaches that the use of peptide antibodies are simple and well established. Thus, the C-terminal portion of hBNP could have been used as the immunogen to produce antibodies specific for the C-terminal region of hBNP. Alternatively, one could have screened for the antibodies specific for the C-terminal region of hBNP because such screening methods are well known in the art and the use of even small peptides of 6-10 amino acids in length (as taught by Hashida), as immunogens, is simple and well established (as taught by Bulinski).

One would have been motivated to produce monoclonal antibodies specific for the C-terminal region of hBNP because Itoh et al., teach monoclonal antibodies specific for the N-terminal region of BNP, such as KY-BNP-II. Hashida and Takeyama et al., provide an expectation of success by teaching that BNP has a high sequence homology with ANP. Thus, production of monoclonal antibodies specific for the C-terminal region of hBNP would allow one to perform sandwich immunoassays, which Harlow et al., teach are one of the most useful immunoassays. Additionally, Harlow et al., teach that the major advantage of the sandwich format is that the antigen does not need to be purified prior to use. Further, it would have been obvious to add the sample to either the labeled or immobilized antibody first, with the subsequent addition of either the labeled or immobilized antibody, which ever was not already added to the sample, because both methods of immunoassay are well known and routine in the art and provide the same results. In addition, the use of either enzymatic or radioisotope labels would have been prima facie obvious because the use of both types of labels was also well known and routine in the art.

It was routine to make and screen for monoclonal antibodies exhibiting the desired specificity at the time the invention was made. Thus, in the absence of evidence to the contrary or in the absence of unexpected results, the production of antibodies having desired specificity and their use in immunoassays would have been *prima facie* obvious to one of ordinary skill in the art.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMW